Editorial Comment

Treatment of Acute Myocardial Ischemia

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The report on myocardial ischemia from the UCLA Department of Medicine (elsewhere in this issue) includes a selective discussion of the mechanisms involved in ischemic injury and emphasizes a series of procedures under investigation for the evaluation, diagnosis and treatment of acute ischemia and evolving myocardial infarction. This is an area of great current interest because of the development of interventions designed to prevent cell death in acute infarction. These include lysis of thrombi in coronary arteries with streptokinase or tissue plasminogen activator, thrombolysis with angioplasty, emergency bypass operations and a new experimental procedure called total vented bypass and regional reperfusion without thoracotomy. This commentary is aimed at providing background information on some of the concepts presented, with emphasis on the biology of ischemia and infarction as it applies to the treatment of acute ischemia in both experimental animals and humans.

Serious efforts to develop therapy for acute myocardial infarction began in the early 1970s with Braunwald and Maroko's popularization of the idea that jeopardized, potentially salvageable myocardium existed for several hours in the left ventricle of dogs and humans with acute myocardial ischemia.[1] It was known from earlier studies that the myocardium of dogs anesthetized for open-chest experiments would tolerate episodes of ischemia of as long as 15 to 18 minutes without necrosis developing. Proof of survival rested on the observation that cell death did not develop in the damaged tissue if it was reperfused with arterial blood. The living myocytes damaged by a brief episode of ischemia were termed *reversibly injured.* After longer periods of ischemia, many of the damaged myocytes died even though the tissue was reperfused and the ischemic state eliminated.[2] These myocytes were defined as *irreversibly injured.* The structural manifestations of lethal injury in ischemic myocytes successfully reperfused with arterial blood have been designated *contraction-band necrosis,* a phenomenon which develops essentially instantaneously in a number of conditions including ischemia and reperfusion (see Ganote for background).[3] These early studies established clearly that not all myocytes in ischemic myocardium die simultaneously.[4] The rate at which cell death occurred in acute regional ischemia in terms of its potential response to treatment was defined by Reimer and Jennings, who showed that necrosis progressed transmurally as a function of the duration of ischemia.[5] The inner layer of the left ventricle dies first; myocytes in the middle and outer layers die sometime later, or not at all. These data formed the basis of numerous studies designed to test whether various drugs would prevent cell death in acute ischemic injury (see Hearse and Yellon for reviews of the topic).[6]

The results of most of these studies of various drug therapies were not convincing because of a variety of problems with the data, including the fact that the initial methods used to estimate infarct size, such as analysis of ST-segment changes or enzyme release into the plasma or enzyme depletion from the area of injury and so forth, proved to be too imprecise and irreproducible. In addition, virtually all early workers failed to recognize that acute myocardial infarcts in animals could vary widely in size under control conditions, and they did not control for the factors that led to the variation. Initially, most papers reported beneficial effects of therapies, including the use of agents as widely diverse as β-blockers, glucose-potassium-insulin, nitroglycerine and steroids. Each agent was reported to reduce some measure of damage resulting from ligation of a coronary artery. In fact, about 80 agents have been reported to reduce infarct size. Few or none of these are used in humans. The scientific world seems to recognize that most of them do not work or do not work sufficiently well to be useful.[6] On the other hand, throughout this period it was clear that cell death resulted from the reduction in arterial flow to the affected myocardium and that cell death could be prevented after varying but brief intervals of ischemia if the arterial flow was restored successfully.

A better understanding of the biology of evolving myocardial infarction occurred in the mid-1970's and developed chiefly because of the development and application of the microsphere technique to the measurement of arterial flow in discrete segments of myocardium.[7] Measurement of arterial flow in ischemic segments by microspheres established the critical role that arterial collateral flow played in ischemic cell death.[5] Results of studies of this type in many laboratories, taken together, established that canine coronary arteries generally were not end arteries and validated the anatomic studies that showed that the various arterial beds of the heart were interconnected in the subepicardial zone by arterioles and often by small arteries[8] but not by capillaries.[9] The arterial connections varied in size from dog to dog, with the result that the volume of collateral flow varied. Thus, dogs with large connections had abundant collateral flow while those with small connections had lesser degrees of flow. In virtually all instances, a subendocardial to subepicardial gradient of flow was present such that the subendocardial layer of the heart received the least and the subepicardial layer the most collateral flow.[5,10] This gradient accompanied the transmural gradient of cell death and is the basis of the general belief that the degree and duration of ischemia are the variables which are most closely associated with the life or death of any given ischemic myocyte. Hemodynamic factors, as well as differ-

(Jennings RB: Treatment of acute myocardial ischemia. West J Med 1987 Jul; 147:62-64)

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Much of the work described in this editorial was supported by National Heart, Lung and Blood Institute grant Nos. HL-23138 and HL-27416.
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ABBREVIATIONS USED IN TEXT

AMPIM = Animal Models for Protecting Ischemic Myocardium
TTC = triphenyltetrazolium chloride

ences in the sensitivity of myocytes in different layers to injury,[11] also contribute to variation in the timing and extent of myocyte death, but the final determinant of survival of individual cells in regional ischemia in vivo appears to be the volume of collateral flow.[4,10]

Failure to recognize the role variations in collateral flow played in infarct size caused much of the variation in results. With small group sizes, it proved to be easy to unintentionally select dogs with low collateral flow and big infarcts in the control group and high collateral flow and small infarcts in the treatment group, especially if the treatment selectively killed off dogs that would have had big infarcts. Much of the remaining variation was due to failure to recognize that the size of the ischemic bed—that is, the amount of myocardium at risk of dying varied from animal to animal. Again, variation was random but was controllable once this variable was recognized. The question of how much necrosis actually had occurred in the ischemic tissue can be answered best by quantitative histologic techniques.[5,10] Although the enzymatic triphenyltetrazolium chloride (TTC) technique underestimates necrosis when the necrosis is focal, it often is used as an unsatisfactory replacement for the slower histologic method. Failure to control for the above variables, together with the use of imprecise, direct or indirect techniques to assess how much cell death actually has occurred, has caused most of the controversy about the effects of therapy in experimental animals.

The National Heart, Lung and Blood Institute supported a study designed to develop appropriate animal models of ischemia in which to test the therapy for acute ischemia—the Animal Models for Protecting Ischemic Myocardium, or AMPIM study. The results of this study established clear guidelines for controlling for variations in collateral flow, infarct size assessment, myocardium at risk and the like.[10] The results of this cooperative study validated methods which finally allowed an investigator to answer the critical question with respect to therapy for acute ischemia: how big would an infarct have been in a heart had no intervention been given?[10] Unless all necrosis is eliminated by the treatment, the variables identified in the AMPIM study should be controlled in any test of the effect of therapy on acute ischemia.

The difficulties I have just described relative to the treatment of acute ischemia in animals in experiments apply to humans as well; however, the human physiology is even more complex. The critical question in humans is the same as it is in experimental animals: how much of the myocardium at risk would have died had an intervention not been given? At present, this question cannot be answered in humans. As in animals, arterial collateral flow is a significant variable; moreover, human hearts exhibit a wide range of collateral development. The hearts of young humans without coronary artery disease have very few collateral connections. They are much like the hearts of pigs[11,12] and probably respond to acute proximal occlusion of a major coronary artery just like the heart of a pig—that is, with transmural severe ischemia and transmural necrosis. Once significant coronary artery disease appears, however, the human heart changes its collateral flow pattern to one much more like that of the dog heart except for the fact that diffuse coronary artery disease often is present and may depress the volume of arterial flow through the collaterals. At any rate, in humans as in dogs, occlusion of a coronary artery usually results in necrosis in the subendocardial region with variable amounts of necrosis in the midepicardial and subepicardial myocardium.[13]

Because of the difficulty of estimating the degree of collateral development in a given patient with ischemia, reperfusion therapy is being tested without an easy or, perhaps, any means of estimating what to expect following occlusion. Is a patient's coronary arterial tree like that of a pig or like that of a guinea pig, in which collaterals are so large that infarcts do not develop after major vessel occlusion?[12] It seems likely to me that reperfusion therapy will not work in patients in whom no collaterals are present unless it is applied very shortly after the onset. On the other hand, more living ischemic myocardium will be available for salvage and for a longer period of time if greater collateral flow is present. This variation in the endogenous condition of the arterial vasculature of the heart makes it difficult to assess the benefit of therapeutic interventions during acute ischemia in dogs and undoubtedly contributes to an even greater variation in the response of patients with coronary artery thrombosis to treatment.

The amount of time during which reversibly injured myocytes are available for salvage by reperfusion is not known in humans and, as indicated, will vary with the volume of collateral flow, hemodynamic and other factors. I have no doubt that moderately ischemic myocytes can be salvaged by successful reperfusion as long as reperfusion has been achieved early enough. If data from reperfusion of animal hearts are transferable to humans, the amount of time during which myocytes can be salvaged is short. Carefully controlled studies in dogs have shown that most myocytes that are going to die in a zone of ischemia are dead after three hours of ischemia have passed and that little or no myocardium is salvageable after six hours of ischemia.[5] Because a dog anesthetized with pentobarbital for an open-chest procedure usually has a high heart rate, elevated blood pressure and so forth, it seems likely that the time available for salvage might be slightly greater in humans than the outer limits given in dogs.

The question of whether reperfusion of myocardium in which no salvageable myocytes are present causes either benefit or additional damage to the heart has not been answered with certainty. The vasculature dies somewhat later than the myocytes, with the result that hemorrhage appears in those parts of the center of the ischemic bed that have been successfully reperfused. Such hemorrhage appears neither to enhance injury nor to depress function in a dog heart. In addition, mildly ischemic myocardium may be present in the heart. Mildly ischemic tissue generally does not die but is nonfunctional and may be electrically unstable as long as the ischemia persists. For example, in dog hearts in which there is significant collateral flow,[5] 20% to 30% of the ischemic myocardium at risk generally survives whether or not the tissue is reperfused. Successful reperfusion of this mildly ischemic tissue will not salvage it in the sense of preventing its death, but will restore aerobic metabolism and contractility and likely remove it as a source of arrhythmias. In the report in this issue, Weiss emphasizes the desirability of restoring ischemic myocardium to an electrically stable state. To the extent that this is achieved in late reperfusion by stabilizing mildly ischemic cells, reperfusion should reduce mortality. Moreover, as noted by Tillisch, results of randomized trials

show less late mortality in the reperfused group of patients. Thus, in addition to salvaging myocytes at risk of death, reperfusion may restore the function of mildly ischemic myocytes that probably would have survived even if no treatment had been given.

The techniques under development by Schelbert and others may yield an objective means of showing that salvage has occurred in successfully reperfused myocardium, especially if the damaged myocytes develop a distinctive metabolic state for which there is an isotopic marker. It is known that reversibly injured myocytes are edematous, have depleted glycogen as well as nucleotide pools[14] and appear to tolerate longer periods of ischemia if the tissue is subjected to repetitive episodes of ischemia separated by periods of reperfusion.[15] Among these various changes might be one which is sufficiently distinctive to allow objective recognition of the fact that living reversibly injured myocytes are present in human myocardium that has been reperfused.

The molecular and physiologic changes developing in ischemia are reviewed briefly by Langer. Although an enormous amount of effort has been directed at identifying the molecular change or changes that cause the cells to die, the precise cause remains unknown. Most of what is known has been developed in studies of totally ischemic myocardium in various in vitro preparations or in severe ischemia in vivo. If the molecular mechanism associated with the transition to lethal injury were known, it might be possible to design a drug specifically to prevent or delay this change and thereby prevent or delay cell death. Even though we lack specific knowledge to design the ideal drug, empiric studies have shown that it is possible to delay the death of severely or totally ischemic myocytes in vivo, such as with cardioplegia, or by pretreatment with agents such as calcium channel blockers.[10] If an agent that would delay cell death could be given prophylactically to the population at risk of infarction, it would allow more time for definitive interventions such as thrombolysis or an emergency bypass procedure.

Knowledge of the biologic changes occurring in zones of moderate-flow ischemia remains scanty. This is the tissue that Buckberg suggests in this report can be salvaged to a greater extent than is possible with restoration of arterial flow alone. In a series of elegant experiments, his group has shown that the degree of functional improvement achieved after episodes of the total ischemia in the K^+-arrested hearts (cardioplegia) can be improved significantly by selective modification of the reperfusate. The modifications have been designed to attack various problems known to be present in ischemia such as cell swelling, excess Ca^{2+} entry, altered capacity to make high-energy phosphate and so forth. He describes treatment of acute regional myocardial ischemia in bypassed hearts using a similarly modified fluid to reperfuse the acutely ischemic myocardial tissue and reports substantial improvements in contractile function of the damaged tissue in hearts subjected to two, four or six hours of regional ischemia. Also, less necrosis was reported to be present when the damaged myocardium was stained with the TTC reaction.

Although the results of these studies appear promising, they do not prove that modification of the circumstances of reperfusion can salvage myocytes that would die if reperfused with unmodified arterial blood. The same problems of collateral flow, myocardium at risk, the use of TTC and the like that have plagued many other workers in this field need to be addressed in these experiments. They should be repeated in a carefully designed protocol that accounts for the previously described chief variables affecting infarct size.

Myocardial ischemia remains an extraordinarily complex phenomenon that is understood only partially. Progress in therapy, however, is encouraging in both humans and animals. The report is very perceptive and summarizes selected aspects of this progress in an authoritative fashion.

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